Emerging Company Profile

Euthymics: Balancing act

By Michael Flanagan
Senior Writer

Euthymics Bioscience Inc. thinks a molecule orphaned by Dov Pharmaceutical Inc. has the right relative ratio of monoamine reuptake inhibition to offer better efficacy and tolerability than marketed antidepressants.

About 60% of MDD patients fail a selective serotonin or norepinephrine reuptake inhibitor (SSRI or SNRI) as first-line therapy, according to President and CEO Anthony McKinney.

"Its not just that they don't work very well, but also people don't tolerate the side effects," he said. These include loss of cognition, sexual dysfunction and weight gain.

McKinney said adding dopamine reuptake inhibition to inhibition of serotonin (5-HT) and norepinephrine reuptake can improve memory and executive function while counteracting deleterious serotonin-induced effects on sexual function and weight gain.

Indeed, the STAR*D study by the **National Institute of Mental Health** showed adding the dopamine and norepinephrine reuptake inhibitor Wellbutrin bupropion to an SSRI was an effective second-line strategy in MDD.

Results were published in the *American Journal of Psychiatry* in 2006. **GlaxoSmithKline plc** markets Wellbutrin.

McKinney said doctors and payers would prefer a single agent to a cocktail, but previous attempts at developing triple uptake inhibitors that were equipotent against each monoamine neurotransmitter have been poorly tolerated.

Euthymics' solution is to fine tune how much a molecule blocks reuptake of the three monoamines. Its amitifadine (EB-1010) is a serotonin-preferring triple reuptake inhibitor that is half as potent for norepinephrine and one-eighth as potent for dopamine.

The compound's effect on serotonergic and norepinephrinergic transmission is similar to that of **Eli Lilly and Co.**'s Cymbalta duloxetine, McKinney said. But it also offers a small amount of dopaminergic activity to counteract the anhedonia (an inability to perceive pleasure) that many MDD patients experience.

Euthymics obtained amitifadine and a preclinical ADHD program by merging with Dov last year. Dov ran into difficulties in 2006 after bicifadine, a norepinephrine and serotonin reuptake inhibitor, failed in Phase III for chronic lower back pain *(see BioCentury, July 26, 2010)*.

Dov had hoped to rebuild around amitifadine and began a 200-patient Phase II trial in late 2007. But, unable to raise money, Dov stopped the trial early and never analyzed the data.

Using a data imputation model to compensate for the study's early stop, Euthymics analyzed results from the first 63 patients and used them to persuade investors to pony up $24 million in a series A round in 2010.

The data showed amitifadine was better than placebo on the primary endpoint of Montgomery-Asberg Depression Rating Scale (MADRS; 18.16 vs. 21.99; p=0.028) and on secondary measures such as Clinical Global Impression-Improvement (CGI-I) scale (p=0.03) and anhedonia factor scores derived from the MADRS (p=0.049).

Amitifadine also had a clean safety profile with no loss in sexual function or weight gain.

Euthymics is now running a Phase IIb/IIIa trial of amitifadine as second-line monotherapy for MDD, with data expected in mid-2012.

The 200-patient TRIADE study uses a sequential parallel comparison design developed by researchers at **Massachusetts General Hospital** and **Harvard Medical School** to reduce the placebo response that has historically hampered clinical trials of antidepressants.

McKinney said the trial is split into two phases of equal treatment duration. In the first phase, more patients are randomized to placebo than to treatment. In the second phase, non-responding placebo patients are re-randomized to treatment or placebo. "The results from both phases are combined, averaging the differences in response rates between active treatment and placebo across the two phases," he said.

Based on TRIADE, McKinney said Euthymics will decide by YE12 whether to partner out some or all of the rights for amitifadine.

"The number of doctors who write the majority of scripts in the U.S. is not as high as you might think, so I could envision a scenario where we offer foreign rights to regional partners and move the product forward on our own in the U.S. — if the IPO window allows it," he said.

Euthymics' second program is a norepinephrine-preferring triple reuptake inhibitor. McKinney said preclinical data for EB-1020 in a juvenile rat model of ADHD will be reported in December.

The plan is to complete a Phase I trial next year.

Euthymics Bioscience Inc.

Cambridge, Mass.

Technology: Selective triple monoamine reuptake inhibitors

Disease focus: Neurology

Clinical status: Phase IIb

Founded: 2009 by Anthony McKinney and Frank Bymaster

University collaborators: Harvard Medical School and Massachusetts General Hospital

Corporate partners: None

Number of employees: 11

Funds raised: $28 million

Investors: Novartis Venture Fund; Venture Investors; H&Q Healthcare Investors; H&Q Life Sciences Investors; GBS Venture Partners; the State of Wisconsin Investment Board; and individual investors

CEO: Anthony McKinney

Patents: 2 issued covering composition of matter and use of amitifadine and related compounds to treat depressive and mood disorders, anxiety, eating disorders and urinary incontinence

COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.

Euthymics Bioscience Inc., Cambridge, Mass.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Harvard Medical School, Boston, Mass.

Massachusetts General Hospital, Boston, Mass.

National Institute of Mental Health (NIMH), Bethesda, Md.